DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Cincinnati District Office
Central Region
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Cincinnati, OH 45237-3097
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August 9, 2006

WARNING LETTER
CIN-06-27353-15

VIA FEDERAL EXPRESS

Mr. Philip L. Carter
President and CEO
Rotech Healthcare, Inc.
2600 Technology Drive
Suite 300
Orlando, FL 32804

Dear Mr. Carter:

On August 1-12, 2005, the Food and Drug Administration (FDA) inspected Rotech Healthcare, Inc.'s, subsidiary, Pulmo-Dose, Inc. (Pulmo-Dose), located at 104 Max Hurt Drive, Murray, KY 42071. Our investigator documented serious violations of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act).

FDA regards traditional pharmacy compounding as the combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the needs of an individual patient. Traditional compounding typically is used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children. It involves providing a service in response to a physician's prescription to accommodate the specialized medical needs of a particular patient. *See Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 360-61 (2002).

All compounded prescription drugs are "new drugs" within the meaning of the FDCA. When a pharmacist compounds a prescription drug, by definition, he or she creates a new drug under federal law because the compounded product is not "generally recognized, among experts . . . as safe and effective." *See* 21 U.S.C. §§ 321(p); Prof'ls & Patients for Customized Care v. Shalala, 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug . . . provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy, Inc., 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), aff'd, Wedgewood Village Pharmacy v. United States, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."); *Weinberger v. Hynson, Westcott & Dunning,* 412 U.S. 619, 629-30 (1973) (explaining the definition of "new drug"). Under the FDCA, a new drug -- including a compounded new drug -- may not be legally manufactured or sold in the United States unless it has been pre-approved by FDA as safe and effective for its intended uses. *See* 21 U.S.C. §§ 321(g) and (p),

352, 353(b), and 355. In virtually every instance, the drugs that pharmacists compound have not been so approved.

FDA has long recognized, however, that traditional pharmacy compounding serves an important public health function by meeting the specialized medical needs of individual patients for whom commercially available approved drugs are inadequate or inappropriate. Accordingly, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments that are not engaged in traditional pharmacy compounding, such as those establishments that manufacture under the guise of traditional compounding large quantities of unapproved new drugs that are commercial copies of approved drugs, or whose compounding practices pose a significant or immediate threat to the public health or to the integrity of the drug approval processes of the FDCA.

FDA's current enforcement policy with respect to compounding of human drugs is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA's Center for Drug Evaluation and Research on June 7, 2002.[1] The CPG lists factors that the agency considers in deciding whether to exercise its enforcement discretion with respect to compounding. One of these factors is whether a firm compounds drugs that are copies, or essentially copies, of commercially available FDA-approved drug products in the absence of a documented patient-specific medical need.

Based on our inspection, we have determined that Pulmo-Dose's operation exceeds the scope of the practice of pharmacy. Our findings indicate that Pulmo-Dose is operating as a pharmaceutical manufacturer and not a pharmacy engaged in extemporaneous compounding. Relevant findings include:

- Pulmo-Dose manufactures budesonide inhalation products in 0.4 mg (1.5 ml vial) and 0.3 mg (1.5 ml vial). However, there is an FDA-approved, commercially available budesonide product (Pulmicort) available in strengths of 0.5 mg and 0.25 mg. We are not aware of any legitimate medical need for these insignificant differences in formulation. Moreover, this concern is especially true given the large numbers of these drugs that you produce, as described below.

- Pulmo-Dose manufactures albuterol 2.5 mg/ipratropium 0.5 mg in 3 ml vials, which is essentially a copy of the commercially available product, DuoNeb. The only noteworthy difference is that Pulmo-Dose's version contains the preservative benzalkonium chloride, and DuoNeb contains edentate disodium. The prescriptions for this product do not specifically call for that particular variation. In addition, your files do not document patient-specific medical need for the variation from the approved product. Thus, there is no demonstration of medical necessity for these compounded products.

- During the first six months of 2005, Pulmo-Dose manufactured and dispensed over [redacted] vials of various inhalation drug products, including over [redacted] vials of budesonide 0.4 mg and over [redacted] vials of formoterol 12 mcg/budesonide 0.5 mg.

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[1] As you may be aware, Section 127 of the FDA Modernization Act of 1997 amended the FDCA by adding section 503A [21 U.S.C. § 353a], which specified certain conditions under which compounded human drugs could be exempt from particular requirements of the Act. In April 2002, however, the United States Supreme Court struck down the commercial speech restrictions in section 503A of the FDCA as unconstitutional. *See Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002). Accordingly, all of section 503A is now invalid. As a result, the agency utilizes its longstanding policy of exercising its enforcement discretion with respect to traditional pharmacy compounding as articulated in Compliance Policy Guide, section 460.200 ("the CPG"), issued on June 7, 2002.

While FDA recognizes that some pharmacists extemporaneously compound reasonable quantities of human drugs upon receipt of valid prescriptions for individual patients, Pulmo-Dose produces a massive amount of unapproved inhalation drugs. In a September 19, 2005, letter to FDA, your legal counsel defends the volume of Pulmo-Dose's operation by pointing to patient-specific prescriptions, albeit prescriptions that often include multiple drugs and extend for months, years, or are "renewed for life." As explained above, though, there is no demonstrated medical need for your compounding of these products that are essentially copies of commercially available drugs. In light of the lack of medical need for these products, this large volume of compounded products goes well beyond the scope of traditional pharmacy compounding and is instead more representative of a drug manufacturer.[2]

In light of the above factors, FDA will not exercise its enforcement discretion for Pulmo-Dose's manufacture and distribution of these products, which are in violation of the following sections of the Act:

Section 505(a) (21 U.S.C. § 355(a))

The inhalation solutions manufactured by Pulmo-Dose are drugs within the meaning of Section 201(g) of the Act (21 U.S.C. § 321(g)). They are also new drugs within the meaning of Section 201(p) of the Act (21 U.S.C. § 321(p)), and may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Act (21 U.S.C. § 355(a)) because no approval of an application filed pursuant to Section 505(b) or (j) of the Act (21 U.S.C. § 355(b), (j)) is in effect for such drugs.

Section 502(f)(1) (21 U.S.C. § 352(f)(1))

Pulmo-Dose's products are misbranded under Section 502(f)(1) of the Act (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for the uses for which they are being offered, and they are not exempt from this requirement under 21 C.F.R. § 201.115.

Section 502(o) (21 U.S.C. § 352(o))

Pulmo-Dose's drug products are also misbranded under Section 502(o) of the Act (21 U.S.C. § 352(o) in that they are manufactured in an establishment not duly registered under Section 510 of the Act (21 U.S.C. § 360), and they have not been listed as required by Section 510(j) of the Act (21 U.S.C. § 360(j)). Your facility is not exempt from registration and drug listing under 21 C.F.R. § 207.10 or

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[2] Your legal counsel also cites the District Court's discussion in *Western States Medical Center v. Shalala* for the proposition that the government has no substantial interest in using volume to differentiate between manufacturing and traditional compounding. *Western States Medical Center v. Shalala*, 69 F. Supp. 2d 1288, 1302-03 (D. Nev. 1999) *aff'd* in part and *rev'd* in part, 238 F. 3d 1090 (9th Cir. 2001), *aff'd sub nom. Thompson v. Western States Medical Center*. But this discussion is simply not applicable to the CPG or FDA's actions regarding Pulmo-Dose. The District Court in *Western States* assessed the Government's interests because the FDAMA provisions at issue restricted commercial speech, and the First Amendment requires a heightened standard of review for regulations of business activities that limit commercial speech. No such infringement of First Amendment rights is at issue when an Agency, exercising its enforcement discretion, considers the volume of drugs that a pharmacy produces. And even if a "substantial interests" analysis were relevant, the Supreme Court in fact concluded that the government has a substantial interest in balancing protection of the Act's new drug approval process by maximizing the number of drugs subjected to it with preservation of compounding in appropriate circumstances. *Thompson v. Western States*, 535 U.S. at 369-70. Significantly, the Supreme Court identified volume-based limitation as a valid way to strike this balance. *Id.* at 372-73.

Section 510(g) of the Act (21 U.S.C. § 360(g)), because it is engaged in the manufacture and distribution of drugs.

Section 501(a)(2)(B) (21 U.S.C. § 351(a)(2)(B))

Deviations from the requirements of 21 C.F.R. Part 211, Current Good Manufacturing Practice (CGMPs) for Finished Pharmaceuticals, were documented during our inspection. These deviations cause your prescription drugs for human use to be adulterated under Section 501(a)(2)(B) of the Act (21 U.S.C. § 351(a)(2)(B)).

At the close of the inspection on August 12, 2005, you were issued a Form FDA-483, Inspectional Observations, which delineated a number of significant deviations from CGMPs which include, but are not limited to:

Failure to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, prior to release as required by 21 C.F.R. § 211.165(a). For example, Pulmo-Dose does not test each batch of drug product to determine conformance with final specifications.

Your attorney's written response of August 30, 2005, addresses the CGMP observations. The response to the above observation is inadequate. As a drug manufacturer, Pulmo-Dose is required to perform finished product release testing.

We have not included observation two of the Form FDA-483 in this letter, regarding process validation of your products, so that you have an opportunity to clarify your attorney's August 30, 2005 response, which is unclear. As a manufacturer of sterile drug products, Pulmo-Dose must conduct process validation as well as validation of the aseptic filling operation. Your attorney's focus on verification testing, which includes sterility testing, visual inspections, and sample assays, does not address the CGMP requirement of validation in the manufacture of these sterile drug products. For your information, you can access FDA guidance through internet link at http://www.fda.gov/cder/guidance/index.htm , including recent FDA information regarding validation and the Sterile Drug Products Produced by Aseptic Processing Guidance released in September 2004. Also, the FDA Compliance Policy Guide (CPG) 490.100 (Validation), can be accessed at http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg.

Your attorney's response to FDA's observation three of the FDA-483, regarding inadequate separation of packaging and labeling, appears to be adequate. This corrective action will be verified at the next inspection.

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to permanently correct these deviations and prevent their recurrence. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

We request that you reply in writing, within 15 working days of receipt of this letter, stating the action that you will take to correct the noted violations, including an explanation of the steps taken to prevent

their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be complete.

Your reply should be directed to the attention of Stephen J. Rabe, Compliance Officer, at the address listed above. If you have questions concerning the violations noted, please contact Mr. Rabe at (513) 679-2700 extension 163.

Sincerely,

Carol A. Heppe
District Director

Cc: Troy S. Adams
Director of Operatations
Pulmo-Dose, Inc.
104 Max Hurt Drive
Murray, KY 42071